REMARKS

Applicants respectfully request entry of the Amendment and reconsideration of the claims. As suggested during the Examiner Interview (summarized below), Applicants have amended claim 1 to recite "comprising administering a therapeutically effective amount of pyridoxal-5'-phosphate for treating cerebral ischemia or ischemic stroke." Support for this amendment can be found throughout the application, including at page 6, lines 9-20; at page 21, lines 5-9; and at page 23, line 28 to page 24, line 29. Applicants respectfully request reconsideration and withdrawal of the rejection under 35 USC § 103(a).

Examiner Interview

Applicants are grateful for the grant and time spent on the personal interview on January 18, 2008, between Dr. Ronald A. Daignault and Mr. David Heller, Applicants' representatives, Mr. Dawson Reimer, Vice-President of Operations for Medicure, Inc. (non-inventor), and Dr. James Charlton, Medicure consultant (non-inventor), with Examiner Phyllis Spivack and Supervisor Arden Marshall. The pending rejection under 35 U.S.C. § 103(a) was discussed. Applicants asserted that there is a difference between reducing stroke incidence by providing an amount of Vitamin B_6 sufficient to bring one up to normal physiological levels compared to administering larger amounts of pyridoxal-5'-phosphate as a therapeutic to treat ischemic stroke and subsequent reperfusion. Also, Applicants put forth why pyridoxine is not interchangeable with pyridoxal-5'-phopshate. It was also suggested that the term "for cerebral ischemia or ischemic stroke" should be added to "therapeutically effective amount". No agreement was reached.

Rejection Under 35 U.S.C. §103(a)

The Examiner rejects claims 1-14 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Jacobs et al., *Stroke* (1999) in view of page 1562 of Goodman & Gilman's The Pharmacological Basis of Therapeutics (9th Ed.). Applicants respectfully traverse the rejection.

To establish a *prima facie* case of obviousness, the prior art reference(s) must disclose or suggest all the claim limitations. MPEP § 2143; *In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991). Although the traditional analysis of obviousness has been modified under *KSR Int'l Co. v.*

Teleflex Inc., 127 S. Ct. 1727 (2007), the Supreme Court still holds that a case of obviousness under 35 U.S.C. § 103(a) still requires the disclosure or suggestion of all claim elements. Applicants respectfully assert that the cited art does not teach or suggest all the claim limitations or provide a reasonable expectation of success. Pyridoxine is distinct from pyridoxal-5'-phosphate. Administration of a therapeutically effective amount pyridoxine has been both toxic and ineffective in treating cardiovascular pathologies. Applicants teach administering a therapeutic amount of pyridoxal-5'-phosphate for treating cerebral ischemia or ischemic stroke and not a nutritionally sufficient amount. Applicants respectfully assert that the Examiner has not sufficiently established a *prima facie* case of obviousness.

To summarize, the Examiner rejects the claims as allegedly obvious due to a prior art observation that administration of vitamin B_6 (pyridoxine) reduces stroke incidence, thereby using pyridoxal-5'-phosphate (P5P) as a therapeutic for treating stroke would be obvious. Applicants respectfully disagree. One can not always assume that a prophylactic or preventative therapy makes obvious a therapy for acute damage. For instance, influenza shots significantly reduce stroke incidence however, influenza shots are not recommended for treating strokes (nor would there be any expectation that such a therapy would be reasonable). Regular exercise reduces stroke incidence but exercise is not recommended as a therapy immediately following the occurrence of cerebral stroke. Applicants respectfully assert that the prior observation does not apply to the instant claims of administering a therapeutically effective amount of P5P for treating cerebral ischemia or ischemic stroke.

Additionally, Pyridoxine is not interchangeable with P5P. As discussed in the previous response, pyridoxine is neurotoxic, and in the literature, it is recommended that adult human doses not exceed 100 mg per day. Second, only limited concentrations of plasma P5P can be achieved by administering pyridoxine. Ubbink et al. (*Am. J. Clin. Nutr.*, 1987) showed that there is no dose dependence of plasma P5P on pyridoxine doses above approximately 40 mg per day of pyridoxine. This has been confirmed by others as discussed in Bor et al.'s paper (*Clin. Chem.*, 2003). Bor et al. proposed that plasma P5P is largely albumin bound and that once the binding to albumin is saturated, the excess P5P is metabolized by alkaline phosphatase to pyridoxal and eventually 4-pyridoxic acid.

Third, the mechanism by which nutritional amounts of vitamin B_6 reduces stroke

incidence is different from a therapeutic use of P5P to reduce ischemic damage. Cardiovascular damage caused by insufficient vitamin B_6 in the diet is caused by excess homocysteine in the plasma. Hyperhomocysteinemia causes damage to the arteries resulting in arteriosclerosis. This plaque formation ultimately leads to heart attacks and strokes due to clot formation at ruptured plaques. The plaques also reduced the artery diameter. P5P is a coenzyme in the process that removes homocysteine from the blood. Administration of 1.2 to 2 mg per day (adult dose) of pyridoxine provides sufficient plasma P5P to return homocysteine to normal levels. This is not the mechanism by which P5P reduces ischemic damage. The mechanism of reduction of ischemic damage occurs at higher plasma concentrations of P5P and has been attributed to the inhibition of P_{2x} receptors, the inhibition of cathepsin, the inhibition of glutaminase and the antioxidant properties of P5P (which are significantly more that of pyridoxine). The difference in mechanism is supported by the dose dependency of reduction in stroke damage included in the patient. There is a significant reduction of stroke damage in rats when the intravenous dose is increased from 10 to 20 to 40 mg/kg/day. It has been previously shown that an adult dose of 1.5 to 2 mg of pyridoxine is sufficient to reduce homocysteine to normal levels and that higher doses have no effect on stroke incidence (Bonaa, 2006, already of record). Therefore the concentration range for a therapeutically effective amount of P5P for treating cerebral ischemia and ischemic stroke is quite different than a nutritionally effective amount.

Applicants respectfully assert that administering pyridoxal-5'-phosphate in therapeutically effective amounts for treating cerebral ischemia and ischemia stroke is not interchangeable with the ingestion of nutritional levels of vitamin B_6 to achieve normal physiological levels. In view of the foregoing, Applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. § 103(a).

Summary

In view of the above amendments and remarks, Applicants respectfully request a Notice of Allowance. If the Examiner believes a telephone conference would advance the prosecution of this application, the Examiner is invited to telephone the undersigned at the below-listed telephone number.

Respectfully submitted,
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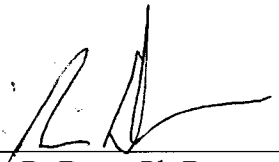
Date: April 29, 2009



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